# Modeling signal transduction networks by continuous and deterministic models

Receptor - ligand binding - assumed to be elementary reaction

Methylation, phosphorylation reactions – catalyzed by enzymes,

Michaelis-Menten kinetics assumed

Dephosphorylation, protein degradation – spontaneous or catalyzed

Protein synthesis –catalyzed by mRNA

Steps: Designate one component as signal and one as response;

Write rates of change for the concentration of components based on the interactions they participate in;

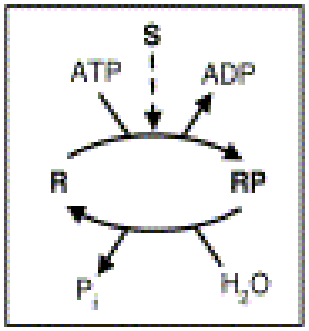
Find steady state concentrations;

Determine the dependence of the steady state response on the signal strength.

# Recall: phosphotransfer cycle

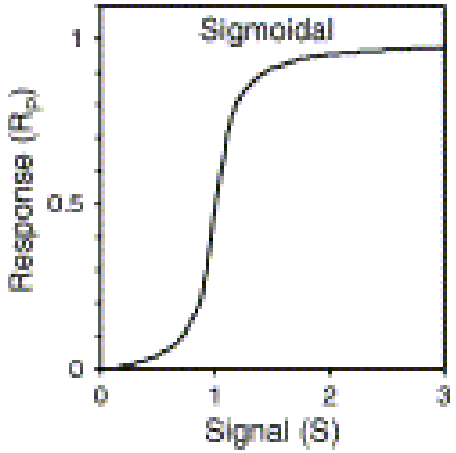
Phosphorylation: protein → phospho-protein, catalyzed by kinase

Dephosphorylation: phospho-protein → protein




Q. Propose an alternative representation of the network. Remember the mass conservation of the protein.

Assume that the phosphorylation and dephosphorylation reactions follow Michaelis-Menten kinetics

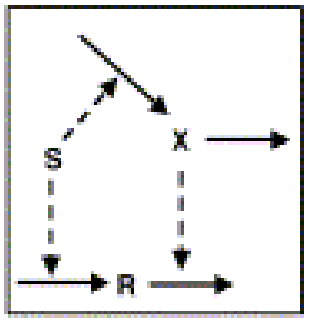



At low values of the signal the protein is predominantly unphosphorylated, while at high values of the signal the protein is predominanty phosphorylated.

J. Tyson, K. Chen, B. Novak, Curr. Opin. Cell Biology 15, 221 (2003)

# Incoherent feed-forward loop

The signal acts on R both directly, and through an intermediary. S is assumed to work at saturation (plentiful substrate). The catalyzed decay is assumed to be elementary (low substrate).




$$\frac{dR}{dt} = k_1 S - k_2 X\ R$$

$$\frac{dX}{dt} = k_3 S - k_4 X$$

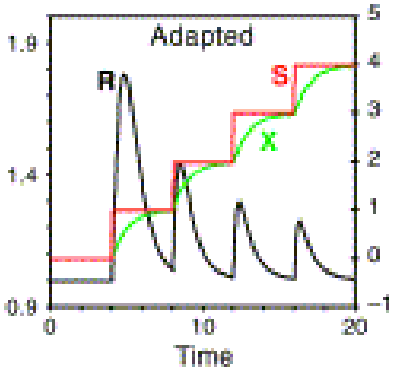
Steady state:

$$X_{ss} = \frac{k_3 S}{k_4}$$

$$R_{ss} = \frac{k_1 k_4}{k_2 k_3}$$

The steady state response does not depend on the signal.

Excitation- adaptation response to step changes in the signal.

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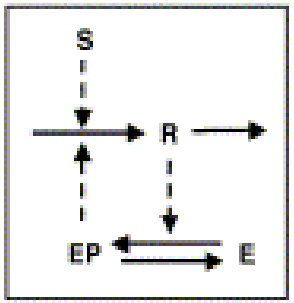
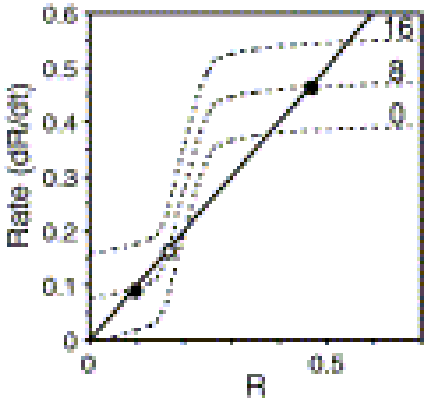
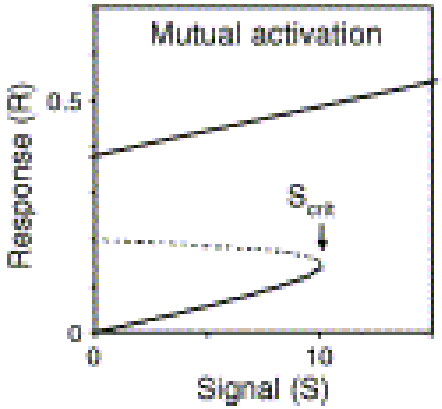
# Positive feedback

R is catalyzing the phosphorylation of E, and $E_P$ feeds back to R. Assume Michaelis-Menten kinetics for the phosphotransfer. Assume E and EP are in a steady state.



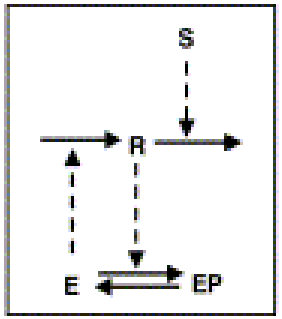

For $S < S_{crit}$ there are three possible steady-state R values.

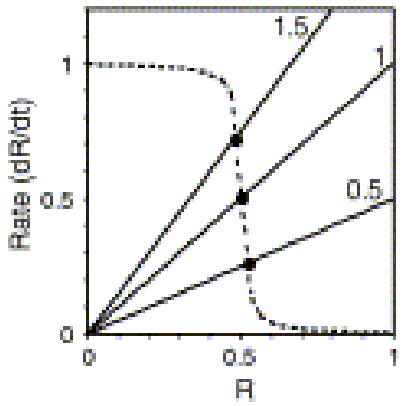
Two of these solutions are stable - bistability

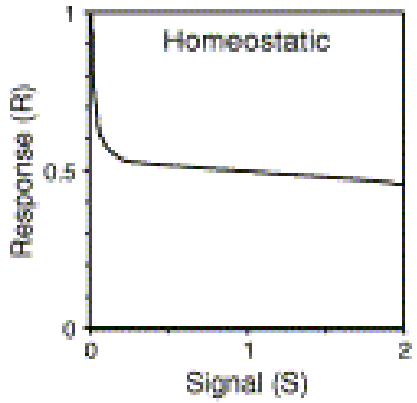
At $S = S_{crit}$ the response increases abruptly and irreversibly – one-way switch

# Negative feedback

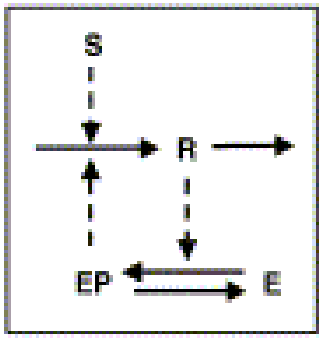
R inhibits the enzyme catalyzing its synthesis.
Assume Michaelis-Menten kinetics for the synthesis of R, and elementary kinetics for the decay of R.
Michaelis-Menten kinetics for the phosphotransfer, E and EP are in a steady state.



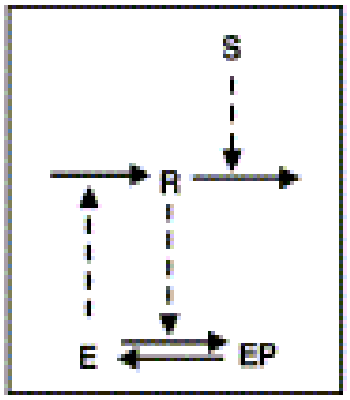




The response depends weakly on the signal – homeostasis.




Positive feedback




Negative feedback

1. What other difference is between these two processes besides the nature of the feedback? Is it important for the end result?

2. The negative regulation in all these examples was taken into account as a catalysis of the degradation process. How would you represent negative regulation of the synthesis?

# Example: Modeling signal transduction in bacterial chemotaxis

System is biologically defined; known motility and excitation- adaptation behavior

Input: concentration of proteins in the signal transduction network

Hypotheses: receptor state (occupancy by ligand, methylation or phosphorylation) determines the efficiency of downstream events

Validation: reproduces known output.

Explored: changes in reaction rates.

Insight: overall behavior is robust to changes in individual rates.

N. Barkai and S. Leibler, Nature 387, 913 (1997)
P. A. Spiro, J. S. Parkinson, H. G. Othmer, PNAS 94, 7263 (1997)
U. Alon et al. Nature 397, 168 (1999)
T. M. Yi et al. PNAS 97, 4649 (2000)

# Continuous and deterministic modeling of gene regulation

mRNA synthesis (transcription) – regulated by transcription factor(s)

Protein synthesis regulated by mRNA

Plentiful substrate for both transcription and translation

Transcription factors may also be regulated post-translationally

Modeling of transcriptional regulation may be broken into two steps:

- Determining promoter occupancy
- Writing the rate of mRNA synthesis as a function of promoter occupancy

# Average promoter occupancy

Single TF: $A + DNA_{free} \underset{k_d}{\overset{k_a}{\rightleftharpoons}} A \bullet DNA$ → bound TF

$$\frac{d\,A \bullet DNA}{dt} = k_a A\, DNA_{free} - k_d .\, A \bullet DNA$$

equilibrium association constant

Steady state: $$A \bullet DNA_{SS} = \frac{k_a}{k_d} A.DNA_{free} = K_A A.DNA_{free}$$

Promoter occupancy: $$Y = \frac{A \bullet DNA}{A \bullet DNA + DNA_{free}} = \frac{K_A.A}{K_A.A + 1}$$

Two cooperative TF: $$Y \approx \frac{K_A.A.K_B.B.K_q}{K_A.A.K_B.B.K_q + 1}$$

cooperativity factor

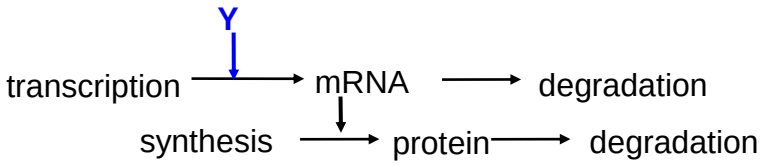
Two coop. binding sites for the same factor: $Y \approx \frac{A^2}{K^2 + A^2}$ , $K^2 = 1/K_q.K_A^2$

Q: What is the shape of the above function?

# Equations for mRNA and protein

$$\frac{d\,mRNA}{dt} = k_t.Y - k_{dm}.mRNA$$

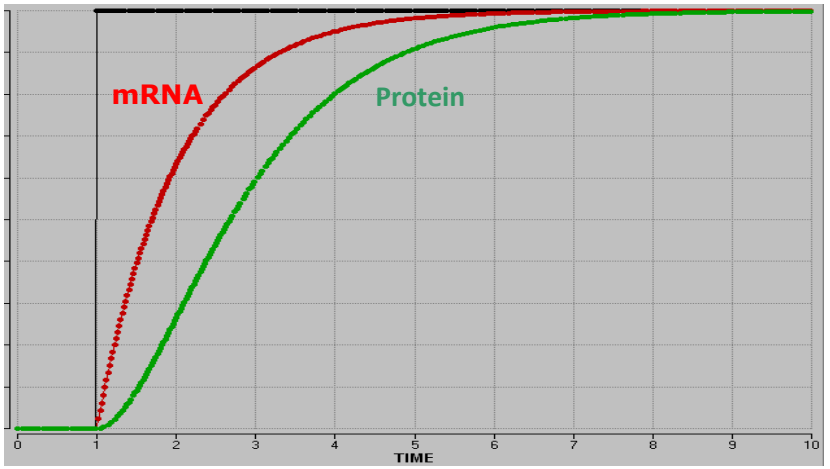
$$\frac{d\,P}{dt} = k_s.mRNA - k_{dp}.P$$




Q. Let's assume that the promoter concentration (Y) is in steady state. How will the steady state mRNA and protein concentrations depend on Y?

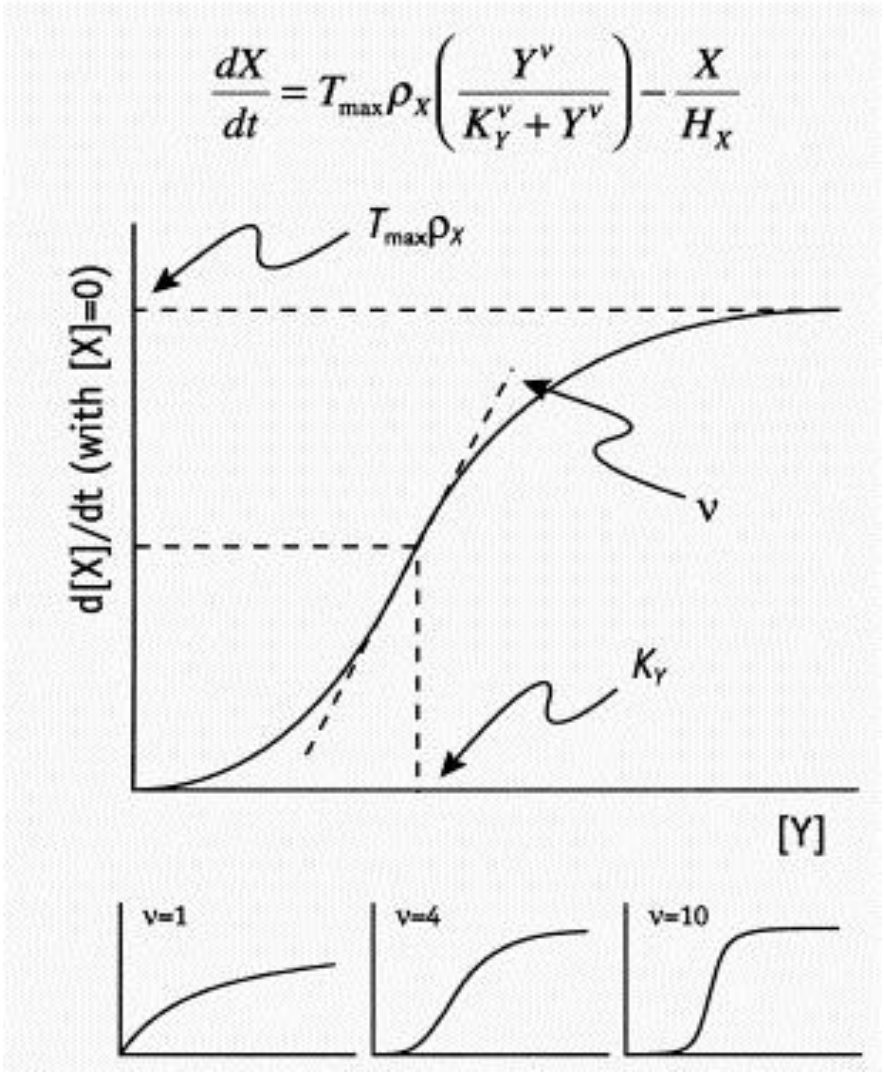
Constitutively present, post-translationally regulated TF: Y switches from 0 to a fixed value at t=0.

$$mRNA(t) = (k_t/k_{dm}).Y.(1 - e^{-t.\,kdm})$$



# General model of transcriptional regulation

$$\frac{dX}{dt} = T_{max}\rho_X\left(\frac{Y^\nu}{K_Y^\nu + Y^\nu}\right) - \frac{X}{H_X}$$

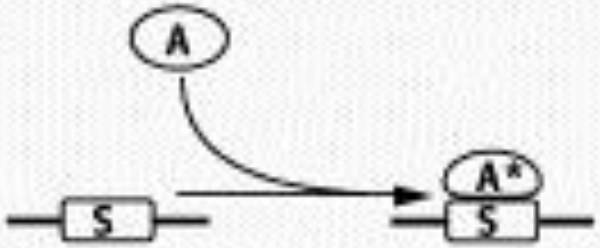



- X – mRNA
- Y – transcriptional activator

- Promoter occupancy akin to cooperative binding by a ν-mer
- Decay is uncatalyzed
- Parameters:
  - maximum rate $T_{max}\rho_X$
  - Half-maximal activity $K_Y$
  - Hill coefficient ν
  - Half- life $H_X$

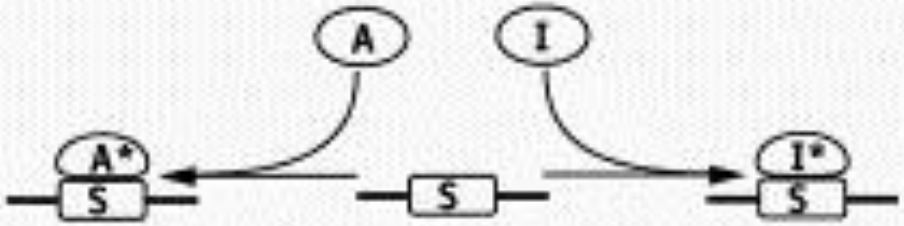
Assumption: combinatorial regulation of synthesis can be approximated with similar sigmoidal curves.

## Transcriptional activation




$$\Phi([A], K_A, \nu_A) = \frac{\left(\frac{[A]}{K_A}\right)^{\nu_A}}{1+\left(\frac{[A]}{K_A}\right)^{\nu_A}} = \left(\frac{[A]^{\nu_A}}{K_A^{\nu_A}+[A]^{\nu_A}}\right)$$

## Competition between a transcriptional activator and a transcriptional repressor




$$[AS] = \frac{\Phi(A)(1-\Phi(I))}{1-\Phi(A)\Phi(I)} = \left(\frac{[A]^{\nu_A}\left(1-\frac{[I]^{\nu_I}}{K_I^{\nu_I}+[I]^{\nu_I}}\right)}{K_A^{\nu_A}+[A]^{\nu_A}\left(1-\frac{[I]^{\nu_I}}{K_I^{\nu_I}+[I]^{\nu_I}}\right)}\right)$$

# Continuous and deterministic modeling of gene regulatory networks

mRNA synthesis (transcription) – regulated by transcription factor(s)

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Transcription factors may also be regulated post-translationally

Steps: Choose an initial condition;

Write rates of change for the concentration of components;

Find steady state concentrations;

Determine the dependence of the steady state response on the initial condition or kinetic parameters.

# Modeling the segment polarity gene network

First: System is  biologically defined; known expression patterns

Input: segment polarity genes, interactions among gene products

Hypotheses: interaction network, transcription factors act as enzymes

Validation: reproduces known gene expression patterns.

Explored: changes in kinetic parameters

Insight: kinetic parameters less important than network topology.

G. von  Dassow et al., Nature 406, 188 (2000)